EXHIBIT 16

Pain Complications of Mesh Surgery

9

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Introduction

Pelvic reconstructive surgery offers many treatments for pelvic organ prolapse. Surgical solutions include vaginal, laparoscopic, and abdominal approaches with native vaginal tissue, fascia autografts and allografts, xenografts, and synthetic absorbable and nonabsorbable mesh. Augmentation of traditional vaginal prolapse techniques using nonabsorbable synthetic mesh demonstrated low morbidity and high anatomic success when initially described. This seemingly reassuring data resulted in the rapid and widespread adoption of such techniques by Gynecologists and Urologists worldwide. Innumerable manufactured products ("kits") for single or multiple compartment prolapse repair are available to pelvic surgeons. Mesh kits have many commonly known advantages such as tension-free placement design, simple technique that is easily repeated with minimal training, and short operative time and disadvantages including price, retraction, adherence, and the potential long-term effect of vaginal atrophy on the health of the mesh implant.

There is no international consensus regarding standard practice of mesh in vaginal surgery. The continuous modifications and rapid introduction of new products make long-term evaluation of any single product challenging. Multiple organizations have cited the insufficient evidence to support mesh in vaginal surgery [1, 2]. The American College of Obstetricians and Gynecologists (ACOG) modified their prior recommendations considering mesh experimental; stating patients considered for vaginal mesh should be informed of the potential complications and lack of long-term data [3]. The Society of Gynecologic Surgeons (SGS) highlighted the lack of reliable evidence to support recommendations regarding the use of mesh for posterior compartment prolapse and stated the risks may outweigh the benefits [4]. Similarly, the Society of Obstetricians and Gynaecologists of Canada (SOGC) stated that the transvaginal mesh devices using trocar placement for prolapse repair should be considered novel techniques and patients should be counseled regarding potential serious adverse sequelae [5]. The Cochrane Collaboration highlighted the insufficient evidence to support the use of mesh repair of posterior compartment prolapse in their recent review [6]. Despite cautionary advice, the enthusiasm surrounding synthetic mesh has continued to increase.

Complications of pelvic reconstruction are generally mild and self-limited (Table 9.1). Pain is a common complication of mesh surgery; however its presentation and clinical implications vary greatly. Pain may initially present in the immediate or delayed postoperative period, varying in quality from mild dyspareunia to severe

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Table 9.1 Dindo classification

Grade	Definition
I	Deviation from the normal postoperative course, requiring therapies such as antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy
II	Additional pharmacological treatments, blood transfusion, or total parenteral nutrition
III	Requiring surgical, endoscopic, or radiological intervention
IIIa	Intervention not under general anesthesia
IIIb	Intervention under general anesthesia
IV	Life-threatening complication requiring ICU management
IVa	Single organ dysfunction, including dialysis
IVb	Multiorgan dysfunction
V	Death of a patient

Adapted from Dindo et al. [42]

debilitating pain rendering the patient unable to sit or walk. Physicians offer medical and surgical options including trigger-point injections, pelvic floor physiotherapy, epidural injections, mesh incisions and excisions, topical and oral medications. Although most patients who undergo mesh placement do not suffer from pain, a number of patients experience a chronic, debilitating pain that is not responsive to these management strategies. Many patients may never experience resolution of pain.

In this chapter we will review the general categories of mesh complications, focusing primarily on pain. Improved understanding of pain after mesh placement is essential to our ability to treat these patients. Evaluation of patients with pain after mesh surgery should take into consideration all contributing factors including mesh properties, surgical methods, and host responses. In this chapter, we will (1) describe the multifactorial etiology of pain after mesh placement; (2) correlate patient symptoms with the anatomy of mesh placement; (3) provide recommendations for evaluation and treatment; (4) suggest strategies to prevent these complications.

Pelvic Reconstructive Surgery

Epidemiology

Pelvic floor reconstruction has gained much interest from the medical field and general population in recent years. From the medical perspective, with a record number of women simultaneously approaching menopause, the healthcare system must anticipate and prepare for the increasing demands on geriatric healthcare. From the population perspective, rising healthcare costs and financial strains in the setting of healthcare reform have left many wondering if they will be able to afford the healthcare they will inevitably require.

According to United States population projections, over 81 million women will be over age 45 by the year 2030, increasing to over 95 million by 2050. After 2030, these women will comprise approximately 23% of the total population [7]. Women have an 11% lifetime risk of undergoing surgical management for pelvic organ prolapse and traditional repair techniques carry a 30% failure risk. This combination of increasing number of patients with prolapse and significant numbers requiring one or more surgeries will result a flood of patients seeking care from pelvic surgeons. The anticipation of this sudden increase in care needs adds additional pressure on the field to develop new techniques with higher long-term success rates.

Risk factors for pelvic organ prolapse have been identified but no preventative care treatment plan is currently in place in the United States. Risk factors include age, parity, obesity, menopause, genetic predisposition, and chronic illnesses that increase pelvic strain. The majority of patients appear to suffer from chronic increased intra-abdominal pressure (i.e., obesity, asthma/cough, constipation) combined with

tissue damage from childbearing. The symptoms of mild prolapse often remain manageable until the hormonal, neurological, and muscular strains of the perimenopausal period combine resulting in a weak and dysfunctional pelvic floor. The combined urologic, gynecologic, and gastroenterological symptom profile brings these patients to medical attention. The challenge of pelvic surgery is not only to recreate pelvic support, but also to rehabilitate lifelong behavioral patterns that have ultimately cumulated in the dysfunction.

Pelvic organ prolapse repair is recommended for symptomatic patients. The treatment of asymptomatic patients is debated amongst experts. Treatment is generally recommended for patients with subjective complaints causing them to seek medical attention or objective findings that require medical intervention. Commonly reported symptoms include vaginal bulge, obstruction of urination or defecation, and dyspareunia. Further discussion with patients may uncover unrecognized symptoms of prolapse including splinting, pelvic pain, and inadequate emptying. Objective findings in patients with prolapse include hydronephrosis, ulceration of prolapsed organs, urinary retention, abnormal pressure-flow urodynamics, or cystoscopic findings of urinary obstruction. Lack of sexual satisfaction is also an indication for prolapse repair, and improvement in sexual function has been demonstrated following pelvic reconstructive surgery [8, 9].

The current definition of pelvic organ prolapse contributes to the discrepancy in subjective symptoms and objective findings. Perfect pelvic organ support is defined as POP-Q stage 0; however, 75% of asymptomatic women have greater than stage 1 prolapse on physical examination. This suggests that 75% of asymptomatic women should be classified as having prolapse. The discrepancy also exists in the evaluation of patients following pelvic organ prolapse repair. Satisfactory surgical outcome is often defined as the pelvic organs higher than 1 cm proximal to the hymen, despite the observation that 40% of women do not meet these criteria, many of whom are satisfied with their surgical outcome.

Materials

Pelvic reconstruction offers a variety of techniques using various combinations of autologous, biologic, and synthetic materials. All areas of prolapse have been addressed in the evolution of pelvic reconstruction including urethral support for stress incontinence, vaginal wall for anterior and posterior wall prolapse, and uterus or vaginal cuff in apical prolapse (Table 9.2).

Autologous vaginal tissue is well tolerated when used in vaginal reconstruction but carries a higher failure rate. When autologous vaginal tissue is utilized in reconstruction for prolapse, the reconstruction carries ~30% risk of recurrence requiring additional surgery. Autologous abdominal wall or fascia lata grafts have improved durability when compared to vaginal grafts. This true human fascia is durable and its use in reconstruction significantly improved long-term anatomic outcome with only 10% failure risk [10, 11]. Pain at the site of graft harvest can be considerable. Additional complications include prolonged immobility due to pain at the harvest site and unfavorable cosmetic outcome. Autologous fascia grafts are also limited by size. Harvest of larger grafts increases the risk of pain, worsens cosmesis, and weakens the harvest site. Therefore, despite the durability of autologous fascia, it is not routinely utilized for repair of pelvic reconstruction.

The use of biological grafts eliminates the pain of autologous harvest. Biological grafts include cadaveric fascia lata and abdominal fascia, and xenografts of dermis or intestine. Biologic grafts are not permanent. Material loss over time has been demonstrated and is due to multiple factors including the intrinsic donor tissue quality, structural changes due postharvest processing, radiation, graft rejection, and reabsorption without remodeling of surrounding tissues.

Synthetic mesh is a part of a surgical evolution attempting to maintain durability of repair while minimizing pain of autologous tissue harvesting. Initially introduced to repair uterine prolapse, synthetic mesh has become the preferred method for repairing pelvic organ prolapse [12]. Synthetic grafts are intended to facilitate minimally invasive

Table 9.2 Materials in pelvic reconstruction

Compartment	Synthetic	Organic
Anterior (urethra)		
Bone-anchored	InFast (AMS)	
Retropubic	SPARC (AMS) Align, Uretex (Bard) Advantage, Lynx (Boston Scientific) T-Sling (Caldera) I-STOP (CL Medical) Supris (Coloplast) TVT, TVT-Abbrevo, TVT-Exact (Gynecare) Sabre (Mentor)	BioArc[a] (AMS) Pelvicol, PelviLace[a] (Bard) Stratasis TF[a] (Cook)
Infrapubic	Ophira (Promedon) INfast Ultra (AMS)	
Obturator fascia	Adjust (Bard) Miniarc (AMS) TVT-Secur (Gynecare/Ethicon)	
Transobturator	Monarc (AMS) Align-TO, Uretex-TO (Bard) Obtryx, Solyx, Uratape (Boston Scientific) T-Sling (Caldera) TVT-O (Gynecare/Ethicon) I-STOP (CL Medical) Aris, Ob-tape (Mentor-Porges)	BioArc-TO[a] (AMS) Pelvicol-TO, PelviLace-TO[a] (Bard)
Anterior (bladder)		
Armed	Perigee (AMS) Avaulta, Avaulta Solo, Pelvitex (Bard) Gynemesh-PS, Prolift, Prolift-M (Gynecare)	Avaulta Plus, PelviSoft[a] (Bard)
Nonarmed	Elevate (AMS) Gynemesh, Prosima (Gynecare)	
Apical (vault, uterus)		
Armed	Avaulta, Avaulta Solo (Bard) Prolift, Prolift-M (Gynecare) IVS Tunneler (Tyco)	Avaulta Plus[a] (Bard)
Nonarmed	Elevate (AMS) Prosima (Gynecare)	
Posterior (rectum)		
Armed	Apogee (AMS) Avaulta, Avaulta Solo, Pelvitex (Bard) Prolift, Prolift-M (Gynecare)	Avaulta Plus, PelviSoft[a] (Bard)
Nonarmed	Prosima (Gynecare)	
Any compartment	Prolene Soft (Ethicon)	Repliform[b] (Boston Scientific) Dermal Allograft[b] (Bard)

[a]Porcine
[b]Human dermis

pelvic organ prolapse repairs using tension-free placement techniques. They provide broad vaginal coverage without the need to trim or suture to the graft directly. Synthetic grafts, like biological grafts, eliminate the risk of painful autologous harvesting but have been associated with prolonged postoperative pain. Mesh is available for prolapse of the anterior, apical, and posterior compartments. Anterior compartment mesh repairs include both trocar-guided and trocarless (also known as single incision) products for repair of urethral hypermobility and bladder prolapse.

Table 9.3 Mesh classification

Type	Pore size	Material	Product	Fiber type
I	Macroporous	Polypropylene	Free Prolene (Ethicon) Marlex (Bard) Kit Apogee, Perigee (AMS) Avaulta (Bard) Prolift (Gynecare)	Monofilament
II	Microporous	Polytetrafluoroethylene (PTFE)	Gore-Tex (Gore)	Multifilament
III	Macro/micro	Polyethylene Polypropylene/polyglactin 910 Polyglactin 910 Polyethylene terephthalate	Mersilene (Ethicon) Vypro (Ethicon) Vicryl (Ethicon)	Multifilament
IV	Submicro	Silicone		Monofilament

Macroporous >75 µm, microporous <75 µm

Table 9.4 Reaction to mesh

Stage	Onset (weeks postoperative)	Reaction	Implication
I	0–2	Inflammation, capillary proliferation, granular tissue formation, giant cell appearance	Critical process for tissue stability, strength
II	0–2	Granular tissue stabilization, lymphocyte appearance	
III	2–4	Inflammation resolves, capillary reduction	Mesh retracts 20–30% during scar formation
IV	4–6	Dense fibrous tissue formation, giant cell presence	

Trocar-guided mesh for the anterior compartment contains four arms, all of which traverse the adductor muscles (two superiorly and two inferiorly). Trocarless mesh for the anterior compartment is fixated intravaginally in two points in the obturator fascia, without penetration of the adductor muscles, and two points in the sacrospinous ligament.

Multiple mesh materials have been used in vaginal reconstruction and some are associated with infection, graft rejection, and pain. Mesh classification systems are utilized in clinical and research settings to describe different mesh materials (Table 9.3). Mesh is categorized by properties that influence the incidence of complications including material, pore size, and fiber type. The first widely used synthetic sling material for urethral prolapse was Mersilene as described in 1962 by Williams and Te Linde [13]. Subsequent published reports of painful erosions and infections of Mersilene stimulated the development of a Silicone sling introduced in 1985 which demonstrated similar complications [14, 15]. Polypropylene was introduced in 1996 and has so far demonstrated the lowest complication rates of all available slings [16]. Pore size is thought to contribute to infection and pain as it relates to the immune system's ability to effectively combat bacterial infection. Mesh surface area has also been implicated in many complications [17], as increased size may increase bacterial contamination, inflammatory response, and release of more noxious degradation products.

Mesh placed in vaginal surgery is not inert [18] (Table 9.4). The active process of tissue incorporation and mesh degradation begins immediately following insertion. This process is responsible for the routine postoperative pain and discomfort that occurs during the first 3 months

following insertion. During the immediate postoperative period, inflammation is followed by the formation of granular tissue. This granular tissue foundation is critical to strength and stability as it is converted into dense fibrous tissue beginning 4–6 weeks following insertion, peaking at approximately 6–12 weeks. Tissue incorporation occurs concurrently with mesh shrinkage. Ultrasound data consistently demonstrates 30–60% decrease in mesh size at 4–12 weeks compared to size at insertion [19]. The concurrent processes of tissue in growth and mesh shrinkage may cause significant pain, particularly in patients who undergo trocar-guided mesh placement. Adherence of the mesh arms in the lateral pelvic wall is a point against which tension increases during the processes of tissue in growth and mesh shrinkage.

Complications of Mesh in Pelvic Reconstructive Surgery

Evaluation of long-term complications after mesh placement is challenging. Multiple trials noted vaginal mesh exposure during postoperative examinations. These patients were treated with a variety of topical medications and office procedures. The early presentation of vaginal mesh exposure resulted in halting of many trials designed to study the outcomes of synthetic mesh grafts. The overall morbidity of this complication is relatively low and does not significantly impact patient's quality of life following mesh placement [20]. Research halted in the early postoperative period due to exposure fails to describe the more severe pain that continues past the immediate postoperative period. Complication evaluation is also hindered by the rapid introduction of novel mesh techniques as complications are identified [21]. For example, the currently available techniques for synthetic mesh placement include armed grafts, nonarmed grafts, absorbable and nonabsorbable sutures, staples, plastic tines, or pressure compression. Given the complexity of pain syndromes as discussed in this chapter, both patients and physicians would benefit from the publication of long-term follow-up data on mesh complications.

Multiple tools exist to monitor the outcomes of mesh placement in reconstructive surgery. In addition to the publication of surgeon experience, organized data collection services monitor complications and publish their findings for public viewing. The Manufacturer and User Facility Device Experience (MAUDE) is a U.S. Food and Drug Administration (FDA) database of voluntarily reported adverse events involving medical devices [22]. Using this data the FDA released a Public Health Notification (PHN) [23] warning physicians and patients on the risks of mesh in vaginal surgery. International data is also being collected, as synthetic mesh use in pelvic reconstruction is not limited to the United States [24].

Perioperative Considerations

Imprecise mesh placement may predispose to complications and vaginal pain. Mesh placed in the vaginal epithelium may cause necrosis and ulceration. Necrotic vaginal tissue will ultimately present as pain, vaginal ulceration, vaginal bleeding, mesh exposure, or dyspareunia. Patients who undergo concomitant vaginal procedures are at risk for this complication due to the extensive dissection of the surrounding vaginal tissues. Similarly, suture line integrity is essential to decreasing the risk of painful complications of vaginal mesh surgery. Wound disruption due to poor suture selection, improper suture placement, or excessive tensioning may result in bleeding under the vaginal wall, infection, and mesh exposure. Synthetic delayed absorbable sutures are most commonly used for closure of vaginal incisions following mesh placement [25]. Polyglactin 910 (Vicryl: Ethicon, Somerville, NJ) and Polyglycolic acid (Dexon: Sherwood/Davis & Geck, St. Louis, MO) are commonly used because they maintain good tensile strength during the initial stages of vaginal healing with minimal inflammatory response.

Perioperative bleeding may contribute directly or indirectly to pain following mesh placement.

Hematoma formation may cause pressure to surrounding tissues and discomfort perioperatively making position change and prolonged sitting uncomfortable. Hematomas may also create sinus tracts, delay healing, and cause wound separation. Vaginal packing is most commonly used to provide local compression and decrease perioperative bleeding immediately postoperatively.

Infection contributes to prolonged pain after mesh placement. Bacterial contamination has been documented during vaginal surgery despite standard infection prevention techniques [26]. Precautions to decrease infection with mesh placement have been described and include preoperative chlorhexidine washes, hair removal, intraoperative administration of intravenous antibiotics, solutions of antibiotics or betadine, sheaths to protect mesh from contamination at insertion, and postoperative oral antibiotics [27]. Mesh contamination in vaginal surgery is similar to contamination after surgical placement of foreign material in other surgical literature [28]. Contamination may result in the formation of biofilms surrounding the mesh which produce a low-grade infection that may not present symptomatically until months following mesh insertion. Symptoms of chronic, low-grade infections caused by biofilms include fatigue, fevers, chills, and constant fluid drainage. These infections may progress to cause pain, visible cellulitis, wound separation, purulent discharge, abscess, or pelvic organ infection including genitourinary, gastrointestinal, or musculoskeletal.

Host tissue characteristics influence the pattern of pain after mesh placement. Neovascularization speed may influence the rate of mesh incorporation and shrinkage. Connective tissue metabolism may influence the rate of degradation and chemical breakdown. Hormonal status has been implicated as a contributing factor to mesh complications; however clinical studies have been inconsistent. In vitro estrogen-deprivation of vaginal and periurethral tissues decreased tissue integrity, which contributes to increase risk of vaginal bleeding, poor wound healing, and susceptibility to infection. Rarely, patients may experience an abnormal foreign body response resulting in a chronic inflammatory process [29].

Etiology of Mesh Pain

Routine postoperative pain is self-limited. The duration of postoperative pain is variable, typically present during the initial stages of healing and shrinkage as mentioned earlier in this chapter. Most often the pain is dull, constant, exacerbated by activity, and relieved with rest or oral pain medications. Increases in intra-abdominal pressure during voiding, defecation, lifting, or intercourse may also exacerbate pain. Treatment for routine postoperative pain should be directed towards relieving the exacerbating factors. Options include local (rest, ice, warm soaks, topical medications) and systemic (oral pain control, stool softeners).

A group of patients will experience an abnormal pain pattern, either pain persisting beyond the routine postoperative period or absence of immediate postoperative pain and appearing weeks after surgery. Initial evaluation of these patients includes a detailed physical examination and relevant diagnostic and imaging studies (detailed later in this chapter). The goal of this evaluation is to identify common complications whose treatment, medical or surgical, may improve or resolve the pain entirely. Mesh removal will successfully improve or resolve pain. Examples of pain complications that are identifiable on initial evaluation include mesh visualization (perforation, erosion, extrusion) and fluid collections (hematoma, abscess). Studies to diagnose these complications include cystoscopy, CT, and magnetic resonance imaging (MRI).

Chronic mesh pain syndrome (CMPS) refers to a complex condition that develops in a small number of patients with pain following mesh reconstruction (Table 9.5). CMPS is characterized by the development of chronic pain symptoms following mesh insertion persisting past the routine postoperative period [30]. This description is consistent with literature describing the onset of other chronic pain syndromes, such as chronic pelvic pain syndrome (CPPS), following multiple initial causative events. Patients with CMPS are identified using the following criteria. First, pain must initiate following mesh placement. A careful history and chart review should be used for confirmation. Second, pain must

Table 9.5 Chronic mesh pain syndrome (CMPS)

Characteristics	Definition
Initiated by mesh	Pain only present following mesh placement
Chronic	Pain past the postoperative period (>90 days)
Refractory	Pain refractory to treatment of identifiable, potentially reversible causes of pain
Disproportion	Pain out of proportion to physical examination findings
Regional symptoms	Presence of ≥1 of the following symptoms, due to neuronal sensitization and cross-talk
Visceral hyperalgesia	Enhanced pain sensitivity in the same and nearby organs
Allodynia	Pain due to stimuli that do not normally provoke pain
Hyperalgesia	Increased response to painful stimuli
Diffuse location	Poorly delineated margins due to relative paucity of nerve endings in viscera
Systemic symptoms	Presence of ≥1 of the following symptoms
Allergic/immunologic	Rash, hypersensitivity, inflammation, fevers
Referred hyperalgesia	Tenderness at remote superficial sites

persist past the routine postoperative period. Pain lasting more than 3 months postoperatively should be considered abnormal. Third, pain must be refractory to medical and surgical treatment of other complications. Patients who present with pain after mesh placement should undergo the recommended examination and testing. Complications should be treated. Patients whose pain persists despite these treatments should be considered for the diagnosis of CMPS. Notably, treatment with mesh removal does not resolve pain. Fourth, pain intensity is considerably greater than routine pain and is not relieved by routine therapies. Pain is out of proportion to physical examination findings. Lastly, regional and systemic symptoms develop as a result of neuronal sensitization, cross-talk, and pain centralization.

Different from self-limiting postoperative pain, CMPS is a pathologic condition caused by the transformation of local vaginal pain into a multiorgan systemic process. Pain should be treated as an ongoing pathologic process instead of a variation of routine postoperative pain. Treatment is challenging given the cascade of events that is not entirely reversible by mesh removal. Risk factors are unknown. A combination of mesh material, surgical technique, and host factors are likely contributors. Multiple case reports and case series have been published to increase awareness of this condition [31].

CMPS is the result of abnormal neuronal activation (Fig. 9.1a). Following the initial event (mesh placement), neuronal up regulation results in simultaneous sensitization of pain pathways in the spinal cord and central nervous system (CNS), along with pelvic organ cross-talk. These abnormal neuronal activation pathways, when continuously stimulated, result in the formation of abnormal somatic-visceral responses. As a result of this pathway, routine postoperative pain driven by pain input is converted to a process whose focus of neural activity is located in the CNS. The long-term peripheral and central release of neurotrophic factors stimulates these sensory pathways resulting in permanent sensory changes, a process referred to as sensitization. Patients who have undergone sensitization often suffer from referred hyperalgesia, visceral hyperalgesia, allodynia, hyperalgesia, and disproportion.

Innervation of Mesh Pain

Pain signals from the pelvic organs travel with somatic nerves, sympathetic and parasympathetic fibers (Fig. 9.1b). Organs located intraperitoneal (ureter, uterus, ovaries, bladder) send pain and temperature signals via the sympathetic nervous system. Preganglionic sympathetic fibers originate at the spinal cord levels T9–L1, exit through the ventral spinal roots, pass through the sympathetic trunks, and synapse at the inferior mesenteric ganglion. Postganglionic fibers

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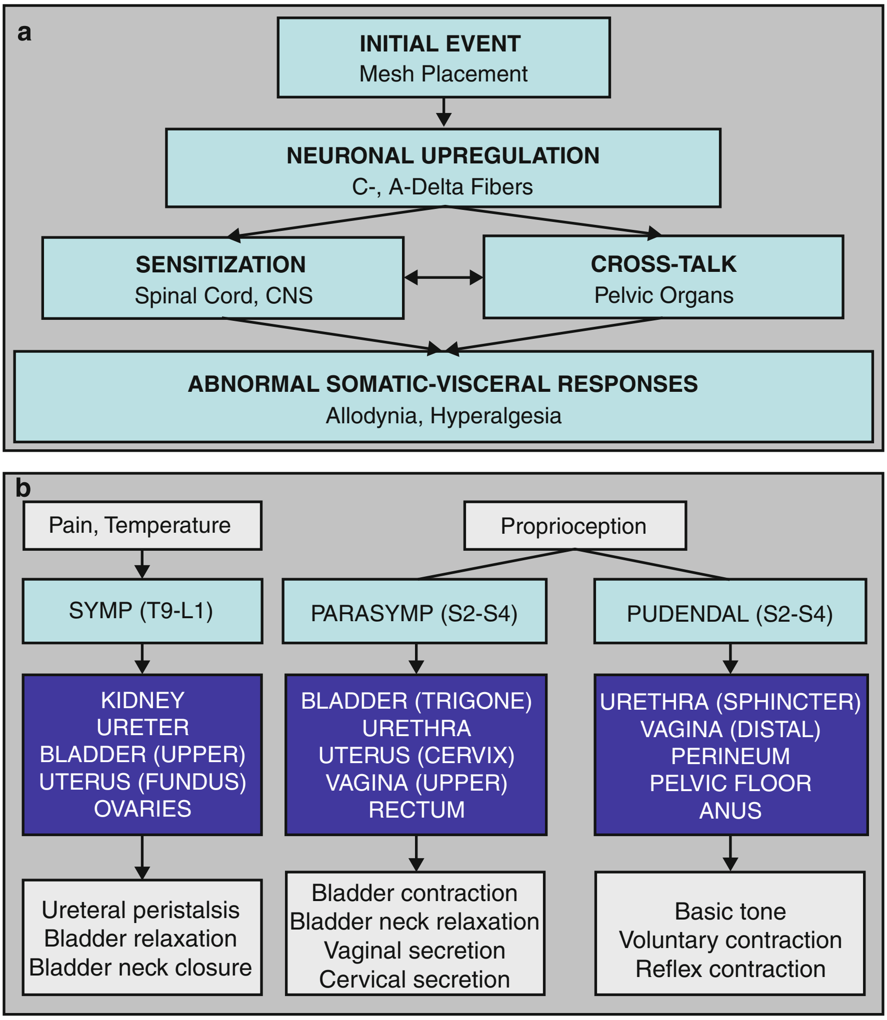

Fig. 9.1 (**a**) Development of abnormal pain responses. Abnormal neuronal activation is a key component of chronic mesh pain syndrome. (**b**) Pelvic innervation. Pain signals from the pelvic organs travel with somatic nerves, sympathetic and parasympathetic fibers

then travel through the superior hypogastric plexus and inferior hypogastric (pelvic) plexus prior to synapsing on the pelvic organs to increase peristalsis, inhibit bladder detrusor contraction, increase bladder neck contractility, and control vasoconstriction.

Parasympathetic pelvic nerves (S2–S4) provide proprioception from the rectum, bladder trigone, urethra, cervix, and upper vagina. These afferent fibers travel through the parasympathetic pelvic splanchnic nerves to the sacral plexus, sensory ganglia, and the ventral spinal cord at level S2–S4. Preganglionic sympathetic fibers originate at the spinal cord level S2–S4, exit through the ventral spinal roots, travel through the sacral plexus, and travel as long pelvic splanchnic nerves until synapsing in the pelvic ganglia. Short postganglionic fibers promote bladder contraction, bladder neck relaxation, and vaginal secretions.

The pudendal, ilioinguinal, and femorocutaneous nerves are often involved in chronic mesh pain. The pudendal nerve (S2–S4) senses proprioception and pain from the distal vagina, urethra,

Table 9.6 Anatomy of mesh pain

Mesh		Etiology of pain			
Location	Organ	Nerve	Muscle	Bone	Viscera
Retropubic	Urethra	Ilioinguinal	Anterior rectus	Pubic symphysis	Urethra Bladder Vagina
Transobturator	Urethra Bladder	Femorocutaneous Posterior cutaneous Pudendal Perineal Inferior anal Obturator	Adductor longus Adductor brevis Adductor magnus Gracilis Obturator externus Obturator internus	Pubic symphysis Ischial rami Ischial spines	Urethra Bladder Vagina
Sacral	Vault Uterus	Sacral roots Lumbosacral plexus Pelvic plexus	Piriformis Obturator internus	Ischial spines Sacrum	Vagina Uterus Rectum
Sacrospinous	Bladder Vault Uterus Rectum	Pudendal Sciatic	Gluteus maximus Levator ani	Ischial spines Ischial tuberosities	Bladder Vagina Uterus Rectum

pelvic floor, and perineum. Efferent fibers provide motor function to the pelvic floor, vagina, perineum, and urethral and anal sphincters. The pudendal nerve courses in close proximity to pelvic organs and can be injured in pelvic reconstructive surgery. The pudendal nerve travels posterior to the sacrospinous ligament and enters the pelvis posterior to the ischial spine, providing innervation to perineal structures including the bulbospongiosus, ischiocavernosus, clitoris, anal canal (including external anal sphincter and puborectalis muscles), and urethral sphincter. The ilioinguinal nerve (L1) may be damaged after passage of trocars through the suprapubic area. The ilioinguinal nerve arises at level T12 and provides sensation to the suprapubic and upper, outer portions of the perineum. Patients who undergo mesh with retropubic trocar entry sites who present with pain should be evaluated for ilioinguinal nerve involvement. The posterior femorocutaneous nerve (S1–S3) originates from dorsal divisions of S1–S2 and ventral divisions of S2–S3 as part of the sacral plexus. The nerve enters the pelvis through the greater sciatic foramen below the piriformis muscle. Branches of the posterior femorocutaneous nerve provide sensation from the posterior thigh, perineum lateral to the labia, and lateral genitalia.

Anatomy of Mesh Pain

A thorough understanding of pelvic anatomy is essential to evaluating complex mesh pain. The identification of mesh pain should trigger evaluation for other related complications (Table 9.6).

Musculoskeletal

Mesh may become incorporated into surrounding muscle. Trauma to the muscle can be directly to muscle fibers or indirectly via traction, local hematoma, and secondary fibrosis causing restriction and pain in movement. Direct muscle injury is less common and more difficult to diagnose. Clinical presentation of mesh pain of the pelvic or extremity muscles includes isolated spasm, pain with position change, or activity-related fatigue relieved by rest. Pain is typically intermittent and activity-related. Pelvic organ muscle involvement may present as dyspareunia or dysfunction of urination or defecation. Mesh placed superficially in the vaginal muscularis instead of the adventitia may cause pain with any manipulation of the vaginal canal and intercourse may be intolerable as a result.

Muscular pain following retropubic mesh placement is primarily a result of trauma to the anterior rectus muscle. Trauma may be direct or

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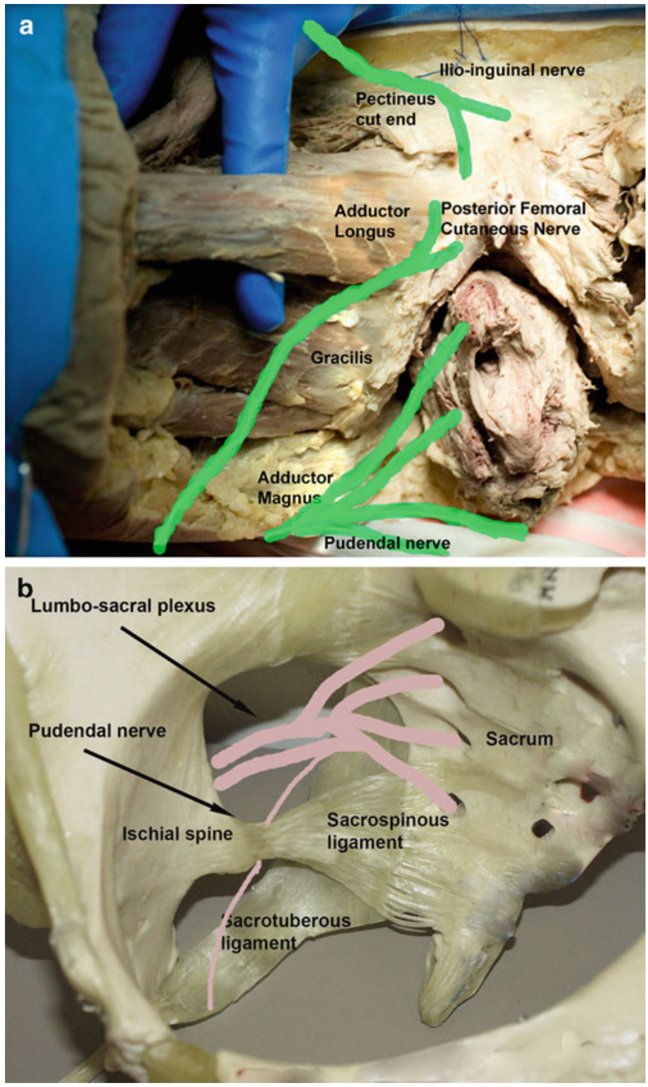

Fig. 9.2 (**a**) Hip adductors. The pectineus, adductor longus, gracilis, and adductor magnus may be involved in mesh pain. Nerves in close proximity are also included. (**b**) Lumbosacral plexus. The lumbosacral nerve, sciatic nerve, and pudendal nerve are particularly vulnerable during apical compartment suspension

indirect as described above. The pain is typically positional and relieved with rest.

Muscular injury after transobturator trocar-guided mesh placement may cause severe pain with walking or joint movement. Obturator muscle involvement presents as pain with abduction, lateral thigh rotation, and walking. The hip adductors are also at considerable risk during placement of a transobturator mesh. The adductor longus, adductor brevis, adductor magnus, gracilis, and obturator externus muscles all originate along the inferior pubic and ischial rami in close proximity to mesh placement (Fig. 9.2a). These muscles are responsible for hip flexion, thigh adduction, medial and lateral rotation. Innervation is provided by the obturator nerve (L2–L4) and sciatic nerve (L4–S3). Pain is exacerbated by movement of the hip and thigh and relieved with rest. The levator ani muscles may also be affected causing pelvic pain, dyspareunia, or pain with prolonged standing.

Pain may occur following apical prolapse repair by multiple techniques. Mesh fixated to the sacrospinous ligament may damage the

surrounding musculature. Involvement of the coccygeus muscle overlying the sacrospinous ligament or the piriformis muscle may be a considerable source of pain. Pain from the levator muscle may occur if placement is inferior to the sacrospinous ligament causing pelvic or gluteal pain radiating to the distal pelvis and vagina. Distal vaginal vault suspensions utilizing the ileococcygeus muscle, or high levator myorrhaphy, may also experience movement-induced gluteal area pain. The piriformis muscle along the anterior sacrum may cause pain after apical compartment repair. Innervation is provided by the piriformis nerve (L5–S2) and functions to laterally rotate the thigh.

Patients who undergo posterior compartment mesh repair with trocar-guided lateral mesh arms may experience pain in the levator muscles or gluteus maximus. Gluteus maximus innervation is provided by the inferior gluteal nerve (S1). Patients may present with pain exacerbated by sitting, external hip rotation and hip extension, Injury to the external anal sphincter muscles may cause pain or defecatory dysfunction including constipation or incontinence of flatus or stool.

Mesh may be anchored to the bony pelvis intentionally or as a result of fibrous adherence following placement. Bone-related mesh pain may be dull or sharp, constant or intermittent. Bone pain after retropubic sling is caused by trocar passage along the posterior aspect of the superior pubic rami posterior to the obturator grove. Trocar passage during placement of a transobturator mesh is in close proximity to the inferior pubic rami. Anterior vaginal wall mesh placed with trocar guidance travels along the lateral inferior aspect of the ischial rami until emerging medially into the vaginal canal just posterior to the descending rami. Physicians are recommended to avoid the superior pubic rami that are in close proximity to the obturator artery and nerve.

Sacral involvement should be suspected in patients with bone pain following sacrocolpopexy. Ischial spines and ischial tuberosities may be damaged during vaginal approaches to posterior compartment repair. Placement of posterior mesh arms in close proximity to these prominences may cause pain by direct trauma or mesh fixation. Patients who have abnormal pain caused by posterior mesh arms report difficulty with prolonged sitting.

Periosteum can be damaged during trocar passage or irritated by infected or adherent mesh causing persistent pain. Mild periosteal inflammation is mild and self-limited and does not require evaluation. Severe localized pubic pain suggestive of osteitis or osteomyelitis requires a diagnostic bone scan. Pain may radiate to nearby muscles.

Visceral

Visceral pain may be caused by trocar placement, mesh penetration, or organ obstruction. Mesh penetration pain is typically dull, constant, and exacerbated by usage of the related organ from muscular inflammation. The affected organ may be in pain with any movement including peristalsis, contraction, filling, or emptying. Pelvic organ prolapse (recurrent or new) may also cause pain or obstruction after mesh placement.

Mesh may penetrate the urethral or bladder after vaginal reconstruction. Hematuria, recurrent infections, and urethral pain that extends past the routine postoperative period is suspicious for mesh penetration and should be evaluated. Detrusor overactivity may be caused by mesh penetration, improper location, or excessive lateral adherence. Urinary obstruction from improper placement may also present as pain. Urinary obstruction following transobturator sling typically requires the patient to lean forward while voiding.

Vaginal mesh complications may present with or without exposure. Palpable mesh cords or bands in the lateral fornices below the vaginal epithelium may present with vaginal pain or be identified incidentally on examination. Mesh folding, shrinkage, and excess tensioning all contribute to formation of mesh cords. Pain with intercourse is also a common complaint following mesh reconstruction.

Mesh penetration into the uterus/cervix may occur following apical prolapse repair. Symptoms include abnormal bleeding, cramping, infections, or pain.

Mesh penetration into bowel or anal sphincter may present as bleeding, infection, obstruction, or incontinence. Patients who report rectal

bleeding postoperatively should be evaluated for mesh perforation. Symptoms including fever, erythema, persistent fullness, or malodorous drainage may reflect an ongoing infectious process. Constant rectal pain, fecal urgency or incontinence, and pain relieved by defecation are signs of rectal obstruction.

Lymphovascular

Perioperative bleeding, recognized or unrecognized, may result in hematoma formation. Up to 25% of patients undergoing retropubic slings have postoperative hematomas visible on MRI [32]. Branches of the obturator vessels may be injured by trocar passage over the superior pubic rami close to the obturator foramen. Trocar passage in the lateral vagina may cause bleeding in branches of the pudendal artery. Hemorrhage from damage to the uterine or internal iliac vessels has also been described.

Chronic inflammatory states following mesh placement can cause an increase in lymphatic fluid production resulting in a chronic increase in drainage. Patients with preexisting poor pelvic venous drainage may also be at risk for pain.

Neurological

Intraoperative nerve damage presents immediately following the procedure. Sharp pain in a specific nerve distribution presenting in the immediate postoperative period suggests intraoperative nerve damage and should be treated. Nerve injury at the time of retropubic mesh placement is rare but has been reported [33]. The most common injury is damage to branches of the ilioinguinal nerve (L1) following lateral skin perforation. Less commonly, incorrect trocar use during retropubic mesh placement may also affect the obturator nerve.

Nerve pain that presents in the postoperative period and persists into the delayed postoperative period should be considered an example of mesh pain and trigger evaluation for other etiologies as well. This includes nerve entrapment and the pelvic organ cross-talk or sensitization.

Transobturator mesh placement may damage branches of the femorocutaneous, posterior cutaneous, pudendal, perineal, inferior anal, or obturator nerve. The obturator internus nerve (L5–S1) innervates the obturator internus muscle that is intentially traversed by trocar-guided mesh products. The anterior, lateral, and posterior femoral cutaneous nerves (L2–S3) provide sensation to the inner aspect of the thigh and lateral perineum where transobturator trocars typically exit the skin. If trocar placement is in close proximity to the labia majora, labial branches of the pudendal nerve may also be involved. The pudendal nerve branches that may be damaged by anterior compartment mesh procedures include the dorsal clitoral nerve (clitoris), posterior labial nerves (posterior labia), and perineal nerves (midperineum). Posterior mesh procedures are more likely to damage posterior pudendal nerve branches such as the inferior anal nerves (perineal body, anus).

Sacrospinous mesh fixation for reconstruction of the apical or posterior compartments may damage multiple pelvic nerves. The lumbosacral nerve plexus on the piriformis muscle, sciatic nerve superolateral to the sacrospinous ligament, and pudendal nerve as it passes posterior to the ischial spines are particularly vulnerable during apical compartment suspension (Fig. 9.2b). Patients with these injuries typically present with buttock or posterior leg pain, loss of sensation, or motor function. Sacrocolpopexy by any approach can cause damage to the presacral nerves at the sacral promontory.

Posterior compartment repair may cause injury to the lumbosacral plexus, sciatic nerve, or pudendal nerve. These nerves are at risk during both trocar-guided and nontrocar-guided mesh procedures. Trocars pathways typically begin at the perineum through the ischial fossa and the levator muscles to the perirectal space.

Evaluation of Patients with Mesh Pain

History

Evaluation of patients with pain after mesh placement begins with a detailed history to identify de novo pain that is discrete from routine postoperative pain as described above. Mesh pain persists past the immediate postoperative period, is activity-related, intense out of proportion to

objective findings, and demonstrates characteristics of CPPS. Whether the etiology of mesh pain is irreversible nerve damage or a progressive pathological pain response remains unclear.

Pain is clearly documented at each visit. The essential details include exacerbating and relieving factors, quality, radiation, severity, and time course. Activities that exacerbate pain are noted; including prolonged sitting or hip flexion, to identify involved musculoskeletal components. Symptoms of obstructive urination, defecation, or dyspareunia suggest misplacement. These findings are often associated with retraction of the vaginal epithelium. Prolonged vaginal, bladder, or rectal bleeding suggests ulceration, infection, or organ penetration. Timing of pain onset in relation to tissue incorporation, mesh breakdown and shrinkage should be considered.

Mesh visualization should be documented using standard nomenclature. A mesh complication categorization scheme has been developed and published by the International Continence Society and the International Urogynecologic Association, and is intended to facilitate communications amongst physicians [34] (Table 9.7). General approach to mesh visualization should take into consideration the time of presentation, symptom severity, and associated symptoms.

Perform a complete review of systems to identify de novo systemic symptoms. Allergic or immune reactions to mesh components may present immediately or in the delayed postoperative period. New diagnoses of systemic illness following mesh placement should alert the physician to consider mesh as a contributing factor. Special notice should be taken when new autoimmune, inflammatory, or allergic illnesses do not respond to traditional management. If available, compare the patients' symptoms to the initial review of systems performed prior to mesh placement. Identify concurrent pelvic complaints of pressure, pain, dyspareunia, and pelvic organ prolapse above the introitus. Patients with these symptoms may have preexisting pain syndromes such as chronic pelvic pain, painful bladder syndrome, interstitial cystitis, fibromyalgia, vulvodynia, dysmenorrhea, and chronic constipation.

Table 9.7 Mesh terminology

Terminology	Definition
Contraction	Reduction in size
Prominence	Parts project beyond a surface
Penetration	Entering
Separation	Physically disconnected
Exposure	Displaying or making accessible
Extrusion	Passage gradually out of a body tissue
Perforation	Abnormal opening into a hollow organ
Dehiscence	Bursting open along natural or sutured lines

Adapted from Haylen et al. [34]

These diagnoses imply a significant component of pelvic floor dysfunction and myofascial pain. Patients with these diagnoses are poor candidates for mesh prolapse repair. Insertion of vaginal mesh with fixation to the pelvic floor will only exacerbate the preexisting condition [35].

Obtain and review Operative Reports and prior History and Physical Examination forms for patients with pain. Complications or intraoperative challenges such as bleeding, prolonged operative time, and intraoperative consultations should be identified. The performance of concomitant procedures and use of other mesh products should also be noted. For example, it is important to obtain information on concomitant procedures with special attention to any discrepancy between planned and performed procedures. Length of antibiotic therapy, prolonged catheter management, blood transfusions, and ICU care are signs of a complicated surgical course.

Minor surgical complications may contribute to mesh pain. Minor complications are generally considered to include hematoma formation, vaginal or urinary infection, or urinary retention. Detailed conversation with the patient regarding the perioperative events may also provide additional information regarding surgical complications.

Obtain detailed information on medical and surgical treatments for pain after mesh placement. Discuss the patient's impression of improvement following these treatments. For

example, patients with pain due to mesh attachment to the levator plate may find relief with anti-inflammatory agents or rest. This pain would be exacerbated by stimulating therapies such as pelvic floor physiotherapy.

Physical Examination

Physical examination is essential to identify the cause of pain. Begin by palpating the path of mesh, tines (if applicable), and location of trocar placement. Identify areas that recreate the patient's pain when palpated. Perform a careful vaginal examination for signs of mesh exposure or erosion. Evaluate the urethra and bladder after mesh for anterior and apical prolapse. Valuable information can be obtained by minimally invasive evaluation methods including postvoid residual for urinary obstruction, bladder filling using indigo carmine for perforation or fistula, cystourethroscopy for perforation, obstruction or misplacement, urodynamics for voiding and storage dysfunction, and voiding cystourethrogram for all indications. Patients who have undergone apical and posterior compartment repairs and present with defecatory dysfunction may require digital rectal examination, sigmoidoscopy, and evaluation of defecatory function using dynamic MRI, or defecography. Patients with de novo rectal bleeding should be evaluated for rectal perforation with sigmoidoscopy.

Ultrasound may provide additional objective information regarding mesh location. Mesh location, direction, size, extrusion, penetration, and folding may be identified by ultrasound. This information may be particularly valuable when Operative Reports are unavailable or when patients have undergone prior mesh incisions or partial excisions (Fig. 9.3a, b).

Complete pelvic imaging may reveal contributing factors for pain. MRI may reveal relevant pathology such as fluid collections, abscesses, prolapse, bone anchors, disc herniation, pelvic masses, and visceral obstruction. However, if intracavitary coils are used, adequate visualization of mesh will not be achieved. Bone scans can also be used to identify signs osteitis or osteomyelitis.

Treatment

Patients presenting with asymptomatic or minimally symptomatic vaginal mesh exposure may present days or years after placement. Mesh visualization identified in the immediate postoperative period is most commonly a direct result of vaginal epithelium separation, or incision dehiscence. Additional attempts at surgical closure may be offered. If the process appears infectious, the mesh may be salvaged with courses of clindamycin or metronidazole. Infections that fail medication management require excision of the prominent mesh portions or total excision to prevent recurrence.

When mesh is visualized in the delayed postoperative period (>6 weeks), this exposure may be due to weakened vaginal epithelium, local infection, chronic inflammation, complications of vaginal healing or mesh shrinkage, or improper placement. Mesh extrusion is typically a result many factors, including but not limited to chronic infection, improper placement, and vaginal atrophy. Vaginal atrophy may be conservatively treated with local or transdermal estrogen. Patients with mesh extrusion who fail medical management should be evaluated for surgical excision of mesh partially or in its entirety. Patients with multiple risk factors for mesh extrusion are more likely to require complete excision given the risk of recurrent extrusion following partial excision.

Mesh incision and partial excision are only recommended for patients with organ obstruction in the absence of pain or infection. Infection is not limited to exposed mesh segments alone. Removing exposed mesh portions in the presence of active infection is followed by recurrent exposure frustrating both patient and physician. Additional surgical attempts at mesh removal become increasingly technically challenging due to mesh retraction and tissue incorporation of remaining portions.

Surgeons treating patients with mesh pain caused by mesh, fixation materials, abscess, or hematoma should be prepared to remove all mesh portions. Partial excision may improve, but is unlikely to completely resolve, mesh pain.

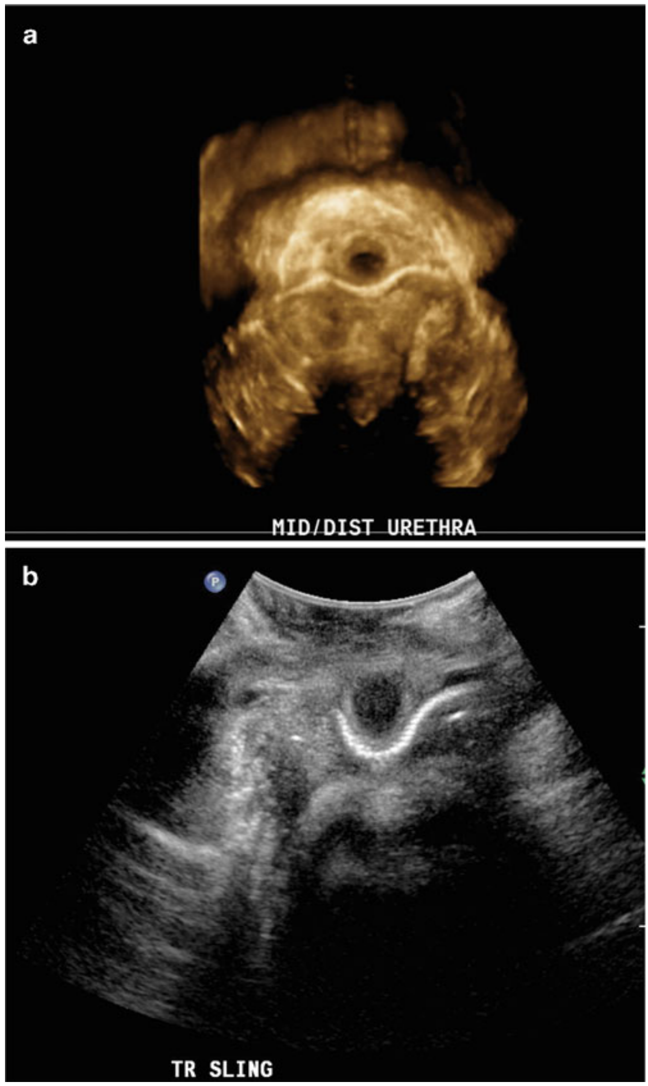

Fig. 9.3 (**a**) 3D ultrasound image for mesh evaluation. Seventy year old G3P3 with lower abdominal pain, urinary retention for 2 years following retropubic sling (TVT). Ultrasound reveals sling in normal position. (**b**) 2D ultrasound image for mesh evaluation. Forty-six-year-old G2P2 with pelvic pain, urinary incontinence, dyspareunia for 1 year following transobturator sling (unknown type). Ultrasound reveals sling with displacement of unilateral arm

Patients with complex mesh pain as described in this chapter receive the maximum benefit from early complete mesh removal to decrease the risk of pain somatization and centralization. Published series note an 88% improvement following mesh removal in patients with severe mesh pain [36].

Technical difficulty of surgical mesh removal is determined by mesh type and location. Armed mesh through the transobturator membrane requires a technically challenging removal. To successfully remove armed mesh segments in their entirety, the obturator membrane must be perforated and dissection carried out laterally. Additional incisions in the lateral thighs may be required to adequately free the arms from the surrounding soft tissues. We suggest preoperatively marking the lateral puncture sites to facilitate intraoperative dissection. If the lateral incisions cannot be identified by patient symptoms or scarring, gentle traction on the medial portion of the mesh arms may be used as a guide. The mesh should be followed from skin incision to the intersection of the adductor muscles and dissected free in a circumferential fashion.

Muscle fibers often must be dissected when mesh has become incorporated into the surrounding fibers. Large defects in the vaginal wall may occur with mesh removal and surgeons ought to be prepared to utilize rotational vaginal flaps, labial flaps, or skip flaps for reconstruction. Following complete healing and resolution of other symptoms such as pain, infection, bleeding, urinary or defecatory dysfunction, evaluation for additional surgery for persistent incontinence or prolapse can begin if clinically indicated.

The decision to proceed with mesh removal for refractory pain should not be avoided due to fear of recurrent incontinence or prolapse. Literature has demonstrated recurrent prolapse following mesh removal may not require immediate surgical correction. Patients who undergo incision of urethral slings are continent in 60% of cases in many large series [37]. Following mesh removal for other compartment prolapse, recurrence is highest for the anterior compartment, which carries a 19% risk of recurrent bladder prolapse. This is consistent with published opinion that fibrotic tissue from mesh placement and its removal is at least as durable as traditional colporrhaphy alone.

Consultations by other physicians may be warranted for patients presenting with illnesses involving other organ systems. However, evaluation and management of the mesh complication must continue. During initial pain evaluation and treatment planning, patients with uncontrolled pain may require Pain Management assistance to select an appropriate medication regimen. The onset of additional symptoms may warrant consultation by Gastroenterology, Rheumatology or Allergy/Immunology. Consultants may provide useful information regarding patient illnesses, however for all illnesses or pain de novo following mesh placement, the authors recommend strong consideration of mesh removal to obtain the best potential to improve patient quality of life.

Despite thorough evaluation and treatment, mesh pain may persist. The centralization of pain may not be completely reversible if sensitization and cross-talk have already created significant abnormal somatic-visceral responses.

Prevention

Intraoperative and perioperative considerations may minimize the risk of mesh complications. Preoperatively, caution should be taken when offering mesh placement at the time of concomitant vaginal procedures to avoid extensive vaginal dissection and increased infection risk. Intraoperative hemostasis and infection prevention are essential. Vaginal packing should be used postoperatively for additional hemostasis and infection prevention.

Litigation is an important concern for physicians inserting vaginal mesh [38]. In addition to adequate preoperative counseling, physicians ought to document discussion with patients regarding the FDA warning on vaginal mesh, and the risks, benefits and alternatives to vaginal mesh reconstruction. Education of both patients and physicians for early signs and symptoms of mesh complications will improve patient selection, outcome, and overall satisfaction.

Conclusion

In conclusion, evaluation and treatment of patients with pain after mesh placement is more complex than previously described. The majority of patients presenting with pain after mesh placement experience a self-limited, routine postoperative pain. However, an unknown number of these patients develop complex mesh pain with symptoms similar to those of CPPS. As an increasing number of patients undergo repair of pelvic organ prolapse with synthetic mesh, physicians must be prepared for the presentation of more complex, multiorgan system complications that may require partial or complete mesh removal. Some patients may never have complete resolution of pain despite mesh removal. The origin of complex mesh pain is unknown. Patients with mesh complications present with a myriad of subjective and objective findings that may be suggestive of a physical reaction to mesh, technical placement complications, or mesh rejection over time.

Management of patients with mesh pain should focus on both physical and emotional recovery. The impact of pain after mesh placement is often underappreciated. Patients must be encouraged to seek support and rehabilitation services in extreme cases. When additional operative interventions are warranted, patients should have appropriate expectations regarding their recovery and be informed of the risk of recurrent pelvic organ prolapse.

Evaluation of the current approach to vaginal reconstruction is warranted. The goal of reconstructive surgery is to provide successful outcomes and to improve quality of life. In searching for improved anatomic outcomes we have adopted synthetic mesh, but at what cost? In a field where treatment success is difficult to quantify [39] and subjective outcomes do not correlate with anatomic outcomes [40, 41], which should prevail? For this reason, these authors share the opinion that successful objective outcome is insufficient reason to continue mesh prolapse repairs in the absence of adequate demonstration of comparably successful subjective outcome.

References

1. Savary D, Fatton B, Velemir L, Amblard J, Jacquetin B. What about transvaginal mesh repair of pelvic organ prolapse? Review of the literature since the HAS (French Health Authorities) report. J Gynecol Obstet Biol Reprod. 2009;38:11–41.
2. Morrisroe S, Lee U, Raz S. The use of mesh in vaginal prolapse repair: do the benefits justify the risks? Curr Opin Urol. 2010;2:275–9.
3. ACOG Practice. Bulletin Number 85, September 2007 (replaces practice bulletin number 79, February 2007). Clinical management guidelines for obstetrician-gynecologists. Am J Obstet Gynecol. 2007;110:707–29.
4. Murphy M. Society of Gynecologic Surgeons systematic review: clinical practice guidelines on vaginal graft use from the society of gynecologic surgeons. Obstet Gynecol. 2008;112:1123–30.
5. Walter J. Transvaginal mesh procedures for pelvic organ prolapse: Society of Obstetricians and Gynaecologists of Canada technical update. J Obstet Gynaecol Can. 2011;33:168–74.
6. Maher C, Feiner B, Baessler K, Adams EJ, Hagen S, Glazener CM. Surgical management of pelvic organ prolapse in women. Cochrane Database Syst Rev. 2007;3:CD004014.
7. United States Census Bureau, 2004. U.S. interim projections by age, sex, race, and hispanic origin. http://www.census.gov/ipc/www/usinterimproj. Accessed 1 Jan 2011.
8. Nieminen K, Hiltunen R, Heiskanen E, Takala T, Niemi K, Merikari M, et al. Symptom resolution and sexual function after anterior vaginal wall repair with and without polypropylene mesh. Int Urogynecol J Pelvic Floor Dysfunct. 2008;19:1611–6.
9. Kuhn A, Burkhard F, Eggemann C, Mueller MD. Sexual function after suburethral sling removal for dyspareunia. Surg Endosc. 2009;23:765–8.
10. Beck RP, Grove D, Arnusch D, Harvey J. Recurrent urinary stress incontinence treated by fascia lata sling procedure. Am J Obstet Gynecol. 1974;120:613–21.
11. Beck RP, McCormick S, Nordstrom L. The fascia lata sling procedure for treating recurrent genuine stress incontinence. Obstet Gynecol. 1988;72:699–703.
12. Huguier J, Scali P. Posterior suspension of the genital axis on the lumbosacral disk in the treatment of uterine prolapsed. Presse Med. 1958;66:781–4.
13. Williams TJ, Te Linde RW. The sling operation for urinary incontinence using Mersilene ribbon. Obstet Gynecol. 1962;19:241–5.
14. Stanton SL, Brindley GS, Holmes DM. Silastic sling for urethral sphincter incompetence in women. Br J Obstet Gynaecol. 1985;92:747.
15. Duckett JRA, Constantine F. Complications of silicone sling insertion for stress urinary incontinence. J Urol. 2000;163(6):1835–7.
16. Rodriguez LV, Raz S. Prospective analysis of patients treated with distal urethral polypropylene slings for symptoms of stress urinary incontinence: 5-year outcomes. J Urol. 2003;170:849–51.
17. Ostergard DR. Polypropylene vaginal mesh grafts in gynecology. Obstet Gynecol. 2010;116:962–6.
18. Clavé A, Yahi H, Hammou JC, Montanari S, Gounon P, Clavé H. Polypropylene as a reinforcement in pelvic surgery is not inert: comparative analysis of 100 explants. Int Urogencol J Pelvic Floor Dysfunct. 2010;21:261–70.
19. Garcia-Urena MA, Vega Ruiz V, Diaz Godoy A, Baez Perea JM, Marin Gomez LM, Carnero Hernandez FJ, et al. Differences in polypropylene shrinkage depending on mesh position in an experimental study. Am J Surg. 2007;193:538–42.
20. Niro J, Phillipe AC, Jaffeux P, Ambiard J, Velemir L, Savary D, et al. Postoperative pain after transvaginal repair of pelvic organ prolapse with or without mesh. Gynecol Obstet Fertil. 2010;38:648–52.
21. Moore RD, Davila GW. Vaginal mesh kits for prolapse 2010: update in technology and techniques to minimize complications. Female Patient. 2010;35:33–7.
22. The Manufacturer and User Facility Device Experience (MAUDE). http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm. Accessed 1 Jan 2011.
23. The United States Food and Drug Administration Medical Device Alerts and Notices on Surgical Mesh. http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm142636.htm. Accessed 1 Jan 2011.

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24. National Institute for Health and Clinical Excellence. Surgical repair of vaginal wall prolapse using mesh 2008. http://guidance.nice.org.uk/IPG267. Accessed 1 Feb 2011.
25. Greenberg JA, Clark RM. Advances in suture material for obstetric and gynecologic surgery. Rev Obstet Gynecol. 2009;2:146–58.
26. Culligan P, Heit M, Blackwell L, Murphy M, Graham CA, Snyder J. Bacterial colony counts during vaginal surgery. Infect Dis Obstet Gynecol. 2003;11:161–5.
27. Darouiche RO, Wall Jr MJ, Itani KM, Otterson MF, Webb AL, Carrick MM, et al. Chlorhexidine-alcohol versus povidone-iodine for surgical site antisepsis. N Engl J Med. 2010;362:18–26.
28. Gristina AG. Biomaterial-centered infection: microbial adherence versus tissue integration. Science. 1987;237:1588–95.
29. Junge K, Bunnebosel M, von Trotha K, Rosch R, Klinge U, Neuman UP, Jansen PL. Mesh biocompatibility effects of cellular inflammation and tissue remodeling. Langenbecks Arch Surg. 2012;397: 255–70.
30. Delavierre D, Rigaud J, Sibert L, Labat JJ. Definitions, classifications and terminology of chronic pelvic and perineal pain. Prog Urol. 2010;20:853–64.
31. Lin LL, Haessler AL, Ho M, Betson LH, Alinsod RM, Bhatia NN. Dyspareunia and chronic pelvic pain after polypropylene mesh augmentation for transvaginal repair of anterior vaginal wall prolapse. Int Urogynecol J Pelvic Floor Dysfunct. 2007;18:675–8.
32. Giri SK, Wallis F, Drumm J, Saunders JA, Flood HD. A magnetic resonance imaging-based study of retropubic haematoma after sling procedures: preliminary findings. BJU Int. 2005;96(7):1067–71.
33. Fisher HW, Lotze PM. Nerve injury locations during retropubic sling procedures. Int Urogynecol J Pelvic Floor Dysfunct. 2011;22:439–41.
34. Haylen BT, Freeman RM, Swift SE, Cosson M, Davila GW, Deprest J, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint terminology and classification of the complications related directly to the insertion of prosthesis (meshes, implants, tapes) & grafts in female pelvic floor surgery. Int Urogynecol J Pelvic Floor Dysfunct. 2011;22:3–15.
35. Butrick CW, Sanford D, Hou Q, Mahnken JD. Chronic pelvic pain syndromes: clinical, urodynamic, and urothelial observations. Int Urogynecol J Pelvic Floor Dysfunct. 2009;20:1047–53.
36. Feiner B, Maher C. Vaginal mesh contraction: definition, clinical presentation, and management. Obstet Gynecol. 2010;115:325–30.
37. Marcus-Brown N, von Theobald P. Mesh removal following transvaginal mesh placement: a case series of 104 operations. Int Urogynecol J. 2010;21:423–30.
38. Mucowski SJ, Jumalov C, Phelps JY. Use of vaginal mesh in the face of recent FDA warnings and litigation. Am J Obstet Gynecol. 2010;203:103.e1–4.
39. Barber MD, Brubaker L, Nygaard I, Wheeler II TL, Schaffer J, Chen Z, et al. Defining success after surgery for pelvic organ prolapse. Obstet Gynecol. 2009;114:600–9.
40. Nieminen K, Hiltunen R, Takal T, Heiskanen E, Merikari M, Niemi K, et al. Outcomes after anterior vaginal wall repair with mesh: a randomized, controlled trial with a 3 year follow-up. Am J Obstet Gynecol. 2010;203:235.e1–8.
41. Withagen MI, Milani AL, den Boon J, Vervest HA, Vierhout ME. Trocar-guided mesh compared with conventional vaginal repair in recurrent prolapse. A randomized controlled trial. Obstet Gynecol. 2011;117:242–50.
42. Dindo D, Demartines N, Clavien PA. Classification of surgical complications. Ann Surg. 2004;244:931–7.